73. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign gene are administered intraperitoneally.

74. (Once Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in said patient, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C, and

further wherein transfection efficiency is increased by at least 50%.

85. (New) The method of claim 38, wherein the foreign gene is a therapeutic gene.

86. (New) The method of claim 69, wherein the foreign gene is a therapeutic gene.

87. (New) The method of claim 74, wherein the foreign gene is a therapeutic gene.

REMARKS

The Invention

The present invention relates to methods for introducing a nucleic acid into cells in a patient. The methods involve administering a cell cycle blocking agent to

the patient and administering the nucleic acid to the patient within seven days of administering the cell cycle blocking agent. The invention further relates to cancer therapy and, in particular, to methods of introducing nucleic acids encoding foreign genes into a cell in a patient having cancer.

Status of the Claims

Applicants wish to thank Examiner Woitach for extending the courtesy of the telephonic interview held on June 17, 2002 with Applicants' representatives Carol Fang and Eugenia Garrett-Wackowski. During this interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. Applicants thank Examiner Woitach for his time.

After entry of this amendment, claims 38-44, 47-54, and 69-87 are pending. Claims 38-44, 46-54, and 69-84 stand rejected in various combinations, under 35 U.S.C. § 112, 35 U.S.C. § 102(b), and 35 U.S.C. § 103(a). These rejections are addressed below. Claim 46 has been canceled without prejudice to future prosecution. New claims 85-87 have been added.

Applicants have amended claims 38, 41-44, 49-54, 69, 71-73, and 74 to recite "foreign gene." Support for "foreign gene" is found in the specification at page 16, lines 10-14. As supported in the specification, "foreign gene" refers to, *inter alia*, exogenous genes not present in the untransformed parental cell or additional copies of endogenous genes present in the untransformed parental cell. Applicants have also amended claims 38, 69, and 74 to recite "wherein transfection efficiency is increased by at least 50%." Support for "wherein transfection efficiency is increased by at least 50%" is found in the specification at page 12, lines 20-24. New claims 85-87 are supported by the claims and specification as filed (*see, e.g.*, page 16, lines 9-17 and claims 38, 69, and 74 as filed). Thus, the amendments do not introduce new matter.

Applicants respectfully request that the amendments of claims 38, 41-44, 49-54, 69, and 71-74 in the present Amendment be entered under 37 C.F.R. §1.114.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner initially maintained the rejection of claims 38-44, 46-54 and 69-84 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement.

As explained previously, determining whether undue experimentation is required by one skilled in the art to practice the invention includes consideration of factors such as the amount of guidance provided in the application and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Furthermore, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The Examiner previously acknowledged that the claims are enabled for "a method of inhibiting the growth of cancer cells in a subject, the method comprising administering an amount of vincristine sulfate and cisplatin in an amount effective to inhibit growth of said cells at or around the site of the tumor, and administering to said cells a polynucleotide encoding a gene which is well known in the art to inhibit cell growth" (*see*, Office Action, page 3), but alleged that undue experimentation is required to enable a method for of enhancing the therapeutic effect of a foreign gene administered to a patient. As discussed during the interview, the present invention relates to methods for introducing a nucleic acid into cells in a patient. Furthermore, as noted by the Examiner during the interview, the present invention is directed to a method of delivering nucleic acids to cells to increase transfection efficiency.

During the interview Applicants discussed several aspects of the rejection with the Examiner. For example, it was pointed out to the Examiner that the

specification provides (1) guidance on methods for delivering nucleic acids to cells, and (2) working examples that unequivocally establish that the claimed methods for ***delivering*** nucleic acids to cells result in increased transfection efficiency.

During the interview with the Examiner, the working examples in the specification were discussed in detail. Specifically, the specification demonstrates that intravenous injection of tumor bearing-mice with OncoTCS (vincristine sulfate encapsulated in sphingomyelin-containing TCS) followed by intravenous injection with a luciferase-encoding-plasmid resulted in up to a 100-fold increase in luciferase expression in normal spleen cells of the mice (*see, e.g.*, page 52, line 23 to page 53, line 31 and Figure 12). The Examiner agreed that this example provided persuasive evidence that the claimed methods are effective for delivering nucleic acids to normal cells ***and*** for increasing efficiency of transfection of the cells by the nucleic acid.

In addition, the Examiner agreed that other working examples in the specification provided persuasive evidence that the claimed methods are effective for delivering nucleic acids to tumor cells. For example, the specification demonstrates that intravenous injection of tumor bearing-mice with OncoTCS followed by intravenous injection with a luciferase-encoding-plasmid resulted in luciferase expression in the tumor cells (*see, e.g.*, page 49, line 23 to page 50, line 5 and page 56, line 3 to page 57, line 8). Transfection efficiency is also enhanced by 10-100 fold when nucleic acids are administered to tumor cells by intratumoral injection of OncoTCS and a luciferase encoding plasmid (*see, e.g.*, page 51, line 10 to page 52, line 21).

Moreover, the Examiner agreed during the interview that the specification is enabled for the claimed methods of inhibiting tumor growth. For example, the working examples in the specification demonstrate that tumor growth inhibition was achieved using intravenous injection of OncoTCS and a plasmid encoding IL-12 (see, e.g., page 54, lines 1-26). Similar results were achieved with OncoTCS and the TK/ganciclovir system with a luciferase-encoding-plasmid (*see, e.g.*, page 54, line 27 to page 55, line 31).

Finally, the specification discloses methods to specifically target the composition comprising the DNA to a cell using a targeting moiety (*e.g.* antibodies, proteins) to a lipid (page 32, lines 11-14). These numerous examples and the disclosure in the specification provide sufficient guidance to one of skill in the art to carry out the claimed methods of introducing a nucleic acid encoding a foreign gene into a cell in a patient, wherein transfection efficiency is increased. Therefore, a skilled artisan, using the teachings of the specification, either alone or together with what is known to those of skill in the art, would be able to practice the invention as claimed, ***without*** undue experimentation. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

The Examiner initially rejected claims 38-44, 46, 47, 49, 52, 69-73, 79, 80, 81, 83, and 84 under 35 U.S.C. § 102(b) as allegedly anticipated by Son *et al.*, *Proc. Natl. Acad. Sci.* (1994), 91:12669-12672.

As explained previously, for a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .***There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.***

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

During the interview, Applicants discussed several aspects of the rejection with the Examiner. As suggested by the Examiner during the interview, independent claims 38 and 69 have been amended to recite a functional limitation of "wherein transfection efficiency is increased by at least 50%." As acknowledged by the Examiner during the interview, the highest transformation efficiency disclosed by Son *et al.* is less than 30%. In addition, Son *et al.* does not teach that any cell cycle blocking agents except cisplatin would be useful for the claimed purpose. Thus, Son *et al.* fail to disclose all of the elements of the claimed methods of introducing a nucleic acid to a cell in a patient, wherein transfection efficiency is increased by at least 50% using the cell cycle blocking agents recited in the claims, and do not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The Examiner initially rejected the claims, in various combinations, under 35 U.S.C. § 103(a) over a number of different references. As explained previously, to establish a *prima facie* case of obviousness, (1) there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. (*See*, M.P.E.P., § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

1. Rejection of claims 38, 53, 54, 69-73, 79, 80, 81, 83, and 84 over Son *et al.* and Roth *et al.*

The Examiner initially rejected claims 38, 53, 54, 69-73, 79, 80, 81, 83, and 84 under 35 U.S.C. § 103(a) as unpatentable over Son *et al.* and Roth *et al.* During the interview, Applicants discussed several aspects of the rejection with the Examiner.

The Applicants' discussion with the Examiner regarding Son *et al.* is discussed in detail above in connection with the 35 U.S.C. § 102(b) rejection. In summary, Son *et al.* does not disclose all of the elements, features or limitations of the presently claimed invention because, in contrast to the present invention, the highest transformation efficiency disclosed by Son *et al.* is less than 30%.

During the interview, it was pointed out to the Examiner that Son *et al.* teach away from the use of drugs other than cisplatin to enhance transfection efficiency. For example, Son *et al.* explicitly states that ***only*** cisplatin significantly sensitizes tumor cells for transfection and that vincristine has no effect on transfection efficiency (*see, e.g.*, page 12671, right hand column). The Examiner agreed that based on this teaching of Son *et al.*, one of skill in the art would not expect that vincristine could be used in method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, wherein transfection efficiency is increased by at least 50%. In addition, during the interview, the Examiner agreed that the increased transfection efficiency demonstrated by the Applicants (see detailed discussion above) was surprising in view of Son *et al.* Thus, if anything, Son *et al.* teach away from the present invention.

Moreover, Son *et al.* teach that ***several*** other anticancer drugs such as methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and carboplatin (a geometric isomer of cisplatin) had no effect on transfection (page 12671, right hand column). Therefore, in view of the teachings of Son *et al.*, one of skill in the art would have ***no motivation*** to use any drug except cisplatin to improve transfection efficiency. Thus, if anything, Son *et al.* teach away from the use of the compounds recited in the claimed invention (*e.g.*, cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid).

Roth *et al.* does not remedy the defect in Son *et al.* In contrast to the claimed invention, Roth *et al.* disclose contacting cells with agents such as cisplatin, doxorubicin, etoposide, verapamil, podophyllotoxin, and 5-fluorouracil (*see,* claims 4, 6, 8, 10, 11, and 12, respectively). Roth *et al.* thus fail to disclose the use of the cell cycle

blocking agents of the claimed invention. Therefore, one of skill in the art would not be motivated to combine the teachings of Son *et al.* and Roth *et al.*

Even if the teachings of Son *et al.* and Roth *et al.* were combined, the combination would not lead to the claimed invention because the references, either alone or in combination, fail to teach or suggest the claimed method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, wherein transfection efficiency is increased by at least 50% using the cell cycle blocking agents recited in the claims.

Absent a teaching or suggestion of a method of introducing a nucleic acid encoding a foreign gene into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Therefore, Applicants respectfully request withdrawal of this rejection.

2. Rejection of claims 38, 48, and 78-84 over Son *et al.*, Roth *et al.*, and Walker *et al.*

Claims 38, 48, and 78-84 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.*, Roth *et al.*, and Walker *et al.* (U.S. Patent 6,041,252). In making the rejection, the Examiner alleges that Walker *et al.* disclose the systemic delivery of agents by means of a liposome and concludes that one of skill in the art would be motivated to combine the nucleic acid and agent in one liposome for a single delivery vehicle. Applicants respectfully traverse this rejection.

As discussed in detail above, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* because Son *et al.* teach away from the claimed invention. Moreover, even if Son *et al.* and Roth *et al.*, were combined, the combination would not lead to the claimed invention. Walker *et al.* do not cure the deficiency of Son *et al.* and Roth *et al.* Walker *et al.* disclose the use of electrical fields to deliver therapeutic agents encapsulated in a liposome (*see e.g.*, Abstract). Walker *et al.* explicitly states that the encapsulated agents directly kill tumor cells and that "agents are administered in multiple cycles to kill cells as they enter the correct cell cycle phase" (*see,* col. 36, lines 15-19). Walker *et al.* contains no mention or suggestion of the use of a

cell blocker or the introduction of a nucleic acid into a cell. Therefore, one of skill in the art would not have had the motivation to combine Walker *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Walker *et al.*, the combination would not lead to the claimed method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, wherein transfection efficiency is increased at least 50% using the cell cycle blocking agents recited in the claims.

Absent a teaching or suggestion of a method of introducing a nucleic acid encoding a foreign gene into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Therefore, Applicants respectfully request withdrawal of this rejection.

3. Rejection of claims 74-77 over Son *et al.*, Roth *et al.*, and Bally *et al.*

Claims 74-77 are rejected under 35 U.S.C. § 103(a) as unpatentable over Roth *et al.* and Son *et al.* as applied to claims 38, 53-73 above, and further in view of Bally *et al.* (US Patent 5,705,385). In making this rejection, the Examiner alleges that Bally *et al.* teach lipid-nucleic acid particles for the delivery and use in gene transfer, in particular the use of PEG-lipid derivative and a G_{M1}-modified lipids to prevent particle aggregation (columns 12-13; bridging paragraph). Applicants respectfully traverse this rejection.

As suggested by the Examiner, claim 74 has been amended to recite "wherein transfection efficiency is increased by at least 50%."

As discussed in detail above, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* because Son *et al.* teach away from the claimed invention. Moreover, even if Son *et al.* and Roth *et al.*, were combined, the combination would not lead to the claimed invention. Bally *et al.* fail to cure this deficiency. Bally *et al.* does not disclose the use of ***any*** claimed cell cycle blocking agents: cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. Moreover, there is no mention or suggestion in Bally *et al.* of the use of a cell

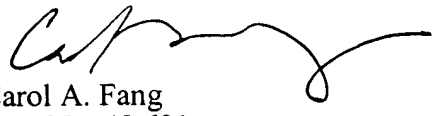
cycle blocking agent. Therefore, one of skill in the art would not have had the motivation to combine Bally *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Bally, *et al.*, the combination would not lead to the claimed method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, wherein transfection efficiency is increased at least 50% using the cell cycle blocking agents recited in the claims.

Absent a teaching or suggestion of a method of introducing a nucleic acid encoding a foreign gene into a cell in a patient as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

38. (Thrice Amended) A method of introducing a nucleic acid [comprising] encoding a foreign [therapeutic] gene into a cell in a patient, said method comprising the steps of

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein transfection efficiency is increased by at least 50%.

41. (Once Amended) The method of claim 38 wherein said foreign gene is a plasmid.

42. (Once amended) The method of claim 38 wherein said foreign [therapeutic] gene comprises a gene selected from the group consisting of genes encoding a cytokine, apoptotic protein, tumor suppressor, heat shock protein, immunogenic antigen, proteinase inhibitor, anti-angiogenic protein, suicide gene for use in GDEPT, ribozyme, antisense nucleic acid, viral protein and a toxin.

43. (Once amended) The method of claim 38 wherein said foreign [therapeutic] gene is administered systemically.

44. (Once amended) The method of claim 38 wherein said foreign [therapeutic] gene is administered locally or regionally.

[46. The method of claim 38 wherein said cell cycle blocking agent is selected from the group consisting of DNA alkylating agents, DNA topoisomerase

inhibitors, microtubule assembly inhibitors, microtubule disassembly inhibitors, DNA-cross linking agents, DNA-binding agents and nucleoside analogues.]

49. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered prior to administering said foreign [therapeutic] gene.

50. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 32 h prior to administering said foreign [therapeutic] gene.

51. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 48 h prior to administering said foreign [therapeutic] gene.

52. (Once amended) A method of claim 38 wherein said foreign [therapeutic] gene is administered prior to administering said cell cycle blocking agent.

53. (Once amended) A method of claim 38 wherein said foreign [therapeutic] gene is administered at least 32 h prior to administering said cell cycle blocking agent.

54. (Once amended) A method of claim 38 wherein said foreign [therapeutic] gene is administered at least 48 h prior to administering said cell cycle blocking agent.

69. (Twice Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid [comprising] encoding a foreign [therapeutic] gene into a cell in a patient having cancer, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered systemically, and wherein transfection efficiency is increased by at least 50%.

71. (Once amended) The method of claim 70, wherein said cell cycle blocking agent and said foreign [therapeutic] gene are administered distal to the site of the tumor.

72. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign [therapeutic] gene are administered intravenously.

73. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign [therapeutic] gene are administered intraperitoneally.

74. (Once Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid [comprising] encoding a foreign [therapeutic] gene into a cell in said patient, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C; and

further wherein transfection efficiency is increased by at least 50%.

85. (New) The method of claim 38, wherein the foreign gene is a therapeutic gene.

86. (New) The method of claim 69, wherein the foreign gene is a therapeutic gene.

87. (New) The method of claim 74, wherein the foreign gene is a therapeutic gene.

APPENDIX B

PENDING CLAIMS SUBJECT TO EXAMINATION

38. (Thrice Amended) A method of introducing a nucleic acid encoding a foreign gene into a cell in a patient, said method comprising the steps of

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein transfection efficiency is increased by at least 50%.

39. (As filed) The method of claim 38 wherein step (b) is performed within 3 days of step (a)

40. (As filed) The method of claim 38 wherein step (b) is performed within 24 hours of step (a).

41. (Once Amended) The method of claim 38 wherein said foreign gene is a plasmid.

42. (Once amended) The method of claim 38 wherein said foreign gene comprises a gene selected from the group consisting of genes encoding a cytokine, apoptotic protein, tumor suppressor, heat shock protein, immunogenic antigen, proteinase inhibitor, anti-angiogenic protein, suicide gene for use in GDEPT, ribozyme, antisense nucleic acid, viral protein and a toxin.

43. (Once amended) The method of claim 38 wherein said foreign gene is administered systemically.

44. (Once amended) The method of claim 38 wherein said foreign gene is administered locally or regionally.

47. (Once Amended) The method of claim 38, wherein said cell cycle blocking agent is selected from the group consisting of cyclophosphamide, taxol, and vincristine.

48. (As filed) The method of claim 38 wherein said cell cycle blocking agent is in a liposome formulation.

49. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered prior to administering said foreign gene.

50. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 32 h prior to administering said foreign gene.

51. (Once amended) A method of claim 38 wherein said cell cycle blocking agent is administered at least 48 h prior to administering said foreign gene.

52. (Once amended) A method of claim 38 wherein said foreign gene is administered prior to administering said cell cycle blocking agent.

53. (Once amended) A method of claim 38 wherein said foreign gene is administered at least 32 h prior to administering said cell cycle blocking agent.

54. (Once amended) A method of claim 38 wherein said foreign gene is administered at least 48 h prior to administering said cell cycle blocking agent.

69. (Once Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in a patient having cancer, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered systemically, and wherein transfection efficiency is increased by at least 50%.

70. (As filed) The method of claim 69, wherein said cancer comprises a tumor.

71. (Once amended) The method of claim 70, wherein said cell cycle blocking agent and said foreign gene are administered distal to the site of the tumor.

72. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign gene are administered intravenously.

73. (Once amended) The method of claim 69, wherein said cell cycle blocking agent or said foreign gene are administered intraperitoneally.

74. (Once Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid encoding a foreign gene into a cell in said patient, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C, and

further wherein transfection efficiency is increased by at least 50%.

75. (As filed) The method of claim 74, wherein said (PEG)-lipid derivative is a PEG-ceramide.

76. (As filed) The method of claim 75, wherein said PEG-ceramide is a member selected from the group of PEG-Cer-C14, PEG-Cer-C20, and PEG-Cer-C8.

77. (Once Amended) The method of claim 74, wherein said lipid derivative is present in an amount of from about 1% to about 20% by weight of the lipid formulation.

78. (New) The method of claim 74, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting said cationic lipid with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

79. (New) The method of claim 38, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

80. (New) The method of claim 38, wherein the nucleic acid is in a lipid formulation.

81. (New) The method of claim 80, wherein the nucleic acid is fully encapsulated in a lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

82. (New) The method of claim 80, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting cationic lipids with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

83. The method of claim 69, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

84. The method of claim 74, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

85. (New) The method of claim 38, wherein the foreign gene is a therapeutic gene.

86. (New) The method of claim 69, wherein the foreign gene is a therapeutic gene.

87. (New) The method of claim 74, wherein the foreign gene is a therapeutic gene.